IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	Eugen Koren and Mirna Koscec		
Serial No:	08/765,324	Art Unit:	1645
Filing date:	December 24, 1996	Examiner:	P. Duffy
For:	METHOD FOR MAKING ANTIBODIES IMMUNOREACTIVE WITH AN EPITOPE OF AN APOLIPOPROTEIN		

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the rejection of claims 48-51 in the Office Action mailed June 18, 2002, maintained in the Advisory Action mailed December 16, 2003, and further to the Decision on Petition dated September 2, 2003. A Notice of Appeal was faxed on August 27, 2003. Please charge the fee for filing of an Appeal Brief with a two-month Extension of Time to Deposit Account No. 50-1868. It is believed that no additional fee is required with this submission. However, should a fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee, Oklahoma Medical Research Foundation, Oklahoma City, OK.

(2) RELATED APPEALS AND INTERFERENCES

Related application U.S. Serial No. 08/970,045 filed November 13, 1997, is also on appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 48-51 are pending and are on appeal. The text of each claim, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

A Petition to Revive and a Notice of Appeal was faxed on August 27, 2003. An amendment was previously submitted with a Renewed Petition to Revive on April 22, 2003. In the Advisory Action mailed December 16, 2003, the Examiner indicated that this amendment would be entered. An Appendix sets forth the claims as pending.

(5) SUMMARY OF THE INVENTION

A method has been developed to make antibodies to lipoproteins and apolipoproteins which react with the apolipoprotein or lipoprotein, regardless of the amount of lipid present (claim 48). A lipoprotein is formed of a protein (called an "apolipoprotein") and lipid bound to the protein (pages 2-3). When the lipid is removed, the lipoprotein is referred to as the "apolipoprotein" (pages 2-3). Appellants' method is based on the discovery that if one removes the lipid ("delipidation") and denatures the protein ("reduction and carboxylation"), then antibodies to the delipidated, denatured protein (or apolipoprotein) will bind to the protein regardless of the amount of lipid present in the lipoprotein form of the apolipoprotein, and regardless of what the lipoprotein is bound to (for example, when it is complexed with other lipids and proteins in the form of a low or high density lipoprotein complex) (page 37, lines 8-19, line 30 to page 38, line 2, lines 17-25). These antibodies are particularly useful in assays of samples such as serum or whole blood in which there are many interfering reactants, that would

normally have to be removed before the sample could be assayed (objects of the invention, page 19).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 48-51 lack written description under 35 U.S.C. §112, first paragraph.

(7) GROUPING OF CLAIMS

Claims 48, 50 and 51 stand together. Claim 49 is specific to monoclonal antibodies, which has been separately used as a basis for rejection by the examiner.

(8) ARGUMENTS

(a) Claims 48-51 do not lack written description under 35 U.S.C. 112, first paragraph.

The Claimed Invention

Appellants claim a method for making antibodies to an epitope of a lipoprotein which reacts with the lipoprotein independently of lipid content and conformation of the lipoprotein, comprising immunizing an animal with a desired apolipoprotein or lipoprotein which is delipidated, reduced, carboxymethylated, and solubilized with a reducing or denaturing agent, wherein all self-aggregated and degraded material has been removed from the delipidated, reduced, carboxymethylated, and solubilized apolipoprotein or lipoprotein.

This methodology is exemplified in the application in Example 2 beginning on page 62, in which a monoclonal antibody (the subject of claim 49) was made to a delipidated, reduced, carboxymethylated, isolated antigen. This monoclonal was then made as a recombinant

antibody, and shown to retain the same specificity, which was both lipid and conformation independent, as shown by Example 12, beginning at page 91.

Claim 50 specifies that the antibodies are reactive with Apo AI, Apo AII, Apo B, Apo CIII, or Apo E. Claim 51 specifies that the antibodies are reactive with HDL, LDL, or VLDL.

The issues framed by the examiner on page 2 of the office action are whether applicants had conception of

(1) the subgenus of solubilization with a reducing or denaturing agent;

(2) removal of all self-aggregated and degraded material;

(3) soluble lipoprotein as an immunizing material;

(4) immunization with an lipoprotein that is delipidated (i.e., an apolipoprotein"), reduced, carboxymethylated and solubilized with a reducing or denaturing agent, that is free from aggregates and degradation productions and

(5) polyclonal antibodies (encompassed within claim 48, not limited to monoclonal antibodies, as claim 49 is so limited).

The pages recited above, page 37, lines 8-19, line 30 to page 38, line 2, lines 17-25, generally convey appellants had conceived of claim 48. However, appellants also reduced to practice each aspect of claim 48, 1-5 of the items listed above. See example 2, beginning at page 62 (bold added for emphasis):

"The MAb to Apo B, HB_3cB_3, was produced by immunizing mice with **Apo B-100 molecules which had been delipidized, reduced, carboxymethylated, and purified by electrophoresis on a polyacrylamide gel containing 8 M urea.**

Delipidized Apo B-100 readily precipitates due to self-aggregation in aqueous media. In addition to the self-aggregation, Apo B-100 is also susceptible to fragmentation during the solubilization procedure (Socorro, L. and Camejo, G.J. Lipid Res., 20:631-645 (1979); Olofsson, S.O. et al., Biochemistry, 19:1059-1064 (1980)). **Therefore, in order to separate self-aggregated and degraded material from the preserved protein, the delipidized, reduced, and carboxymethylated Apo B-100 was electrophoresed on a polyacrylamide gel containing 8 M urea.** Coomassie blue staining of the urea-polyacrylamide gel revealed three distinct bands. The most prominently stained band in the urea-containing polyacrylamide gel was cut out immediately after the completion of electrophoresis and subcutaneously injected (while still in the gel) into mice without further manipulation of addition or adjuvants. **The most prominently stained band on the urea-polyacrylamide gel had previously been shown to be pure Apo B-100**, as confirmed by eluting the band from the urea-containing gel and electrophoresing it under reducing and denaturing conditions on a standard SDS-containing polyacrylamide gel. The SDS-gel revealed a single protein band of the expected mobility of Apo B-100.

Approximately 10 to 20 μg of the Apo B-100 band excised from the urea-containing gel was injected four times at various locations over a period of two months. The mice immunized with the Apo B-100 according to this procedure

were then used in standard methods to produce hybridomas. Out of forty-two hybridomas which produced MAbs that bound Apo-B-100, only one, HB_3cB_3, **produced a MAb that bound exclusively to LDL**, as shown in Table 3, below."

With respect to "d", production of polyclonal antibodies, immunization of an animal with an antigen will always produce polyclonal antibodies. One must then isolate spleen cells and fuse these with immortal cells, which are then screened, for production of monoclonal antibodies.

With respect to the issue of "lipoprotein" versus "apolipoprotein", any one skilled in the art would understand that when one delipidates a lipoprotein, one by definition obtains an apolipoprotein. It is therefore irrelevant whether one starts with a lipoprotein or an apolipoprotein, one will utilize the same material as an antigen.

The mere fact that there is only examples of two different antibodies which are conformation and lipid independent having been made to a delipidized and reduced antigen does not mean that applicants are not entitled to broader claims under the written description requirement of 35 U.S.C. 112. Moreover, the application does not describe antibodies only to a single antigen, Apo B-100, but also refers to antibodies to other apolipoproteins including Apo A-I, which are lipid independent. See page 28, lines 1-16.

The Legal Standard for Compliance with Written Description

The law has long allowed an applicant to claim all that he is entitled to, not forcing him to limit his claims to a specific example, if other means for achieving the same step would be known to those skilled in the art and not require undue experimentation. That is clearly the case

here.

The most recent articulation of the requirement under 35 U.S.C. 112, for written description, was made by the Court of Appeals for the Federal Circuit in its decision in Amgen Inc. v. Hoechst Marion Roussel, Inc and Transkaryotic Therapies, Inc, 314 F3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003).

> "Section 112 of the patent statute describes what must be contained in the patent specification. Among other things, it must contain "a written description of the invention, and of the manner and process of making and using it . . . [such] as to enable any person of ordinary skill in the art to which it pertains . . . to make and use the same . . . ." 35 U.S.C. § 112 ¶ 1. Thus, this statutory language mandates satisfaction of two separate and independent requirements: an applicant must both describe the claimed invention adequately and enable its reproduction and use. See Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)."
>
> "The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Id. at 1561, 19 USPQ2d at 1115 (citation omitted). **Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan.** Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d

1961, 1966 (Fed. Cir. 1997) ("The description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" Enzo Biochem v. Gen-Probe, Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) (citation omitted)."

"Indeed, the district court's reasoned conclusion that the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, renders Eli Lilly listless in this case. Amgen, 126 F. Supp. 2d at 149, 57 USPQ2d at 1507."

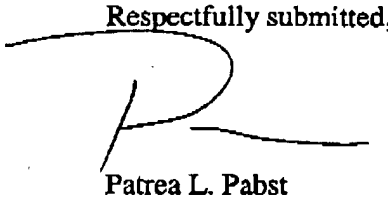
Analysis

When one compares the facts in this case with the legal analysis of the court, discussed above, it is clear that appellants's claims are fully supported under 35 U.S.C. 112, first paragraph. The application has a long discussion of all of the various known apolipoproteins and which lipoproteins they form. The application describes how to specifically delipidated, reduce, carboxylate, and isolate antigen, as well as how to immunize animals, obtain polyclonal antibodies, and screen for the desired specificity. The application demonstrates how to make monoclonal antibodies, and recombinant antibodies with the same specificity. Nothing more is required.

(9) Summary

The Courts have clarified the requirements of 35 U.S.C. 112, written description, to require that one demonstrate conception in the application as filed. There is no requirement for multiple examples, or even a single example, although appellants have provided not only a general conception, but detailed exemplification of multiple actual examples. Each one of the examiner's "requirements" are present in the application. The Board is earnestly solicited to reverse the rejection of all of claims 48-51.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: December 29, 2003
Holland & Knight LLP
One Atlantic Center Suite 2000
Atlanta, GA 30309-3400
(404) 873-8473
fax (404) 873-8588

APPENDIX

48. (previously presented) A method for making antibodies to an epitope of a lipoprotein which reacts with the lipoprotein independently of lipid content and conformation of the lipoprotein, comprising

immunizing an animal with a desired apolipoprotein or lipoprotein which is delipidated, reduced, carboxymethylated, and solubilized with a reducing or denaturing agent, wherein all self-aggregated and degraded material has been removed from the delipidated, reduced, carboxymethylated, and solubilized apolipoprotein or lipoprotein.

49. (previously presented) The method of claim 48 further comprising

isolating the spleen from the immunized animals,

producing hybridomas from the spleen, and

screening the hybridomas for binding to the desired apolipoprotein or lipoprotein.

50. (previously presented) The method of claim 49 for making antibodies to a desired apolipoprotein wherein the apolipoprotein is selected from the group consisting of Apo AI, Apo AII, Apo B, Apo CIII, and Apo E.

51. (previously presented) The method of claim 49 for making antibodies to a lipoprotein wherein the lipoprotein is selected from the group consisting HDL, LDL, and VLDL.

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